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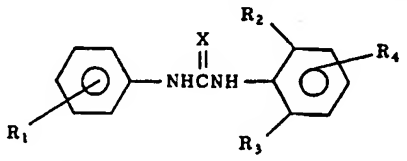
MITSUBISHI KASEI CORP *EP -405-233-A
23.04.90-JP-106986 (+JP-152594) (02.01.91) A61k-31/17
C07c-275/28 C07c-335/16

New di:phenyl:urea deriv. - which reduces lipid and cholesterol levels and are used to treat hyperlipaemia and atherosclerosis

C91-003767 R(AT BE CH DE DK ES FR GB GR IT LI LU NL SE)

B(10-A13A, 10-A13D, 12-G1B2, 12-H3)

Diphenyl urea derivs. of formula (I) are new



(I)

R_1 = 5-18C alkyl;
R_2, R_3 = 1-5C alkyl or alkoxy, or halo;
R_4 = H, 1-5C alkyl or alkoxy, or halo;
X = O or S.

MORE SPECIFICALLY
R_1 = 6-10C alkyl at 2- or 4-position;
R_4 = H.

USE/ADVANTAGE

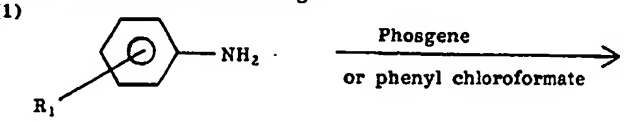
(I) are acylcoenzyme cholesterol acyl transferase inhibitors, and thus reduce the cholesterol level in blood and so are useful for treating hyperlipaemia and atherosclerosis.

Admin. is pref. oral at a dosage of 1-1000 mg/day.

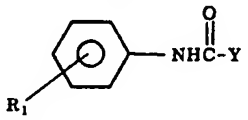
PREPARATION

8 Methods are claimed e.g.

(1)



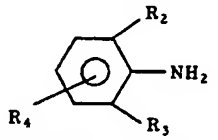
(II)



EP-405233-A+

Ar(IV), organic amine → (I; X = O)
0-100°C, inert solvent

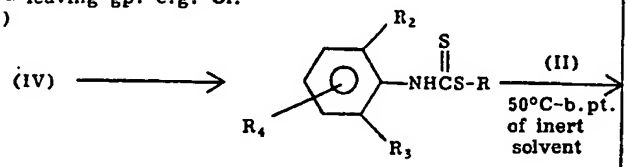
Ar =



(IV)

Y = leaving gp. e.g. Cl.

(2)



(I; X = S)

EXAMPLE

4-octylaniline (1.21 ml) was added to a toluene soln. of 0.50 M 2,6-dichlorophenyl isocyanate (10.6 ml) at room temp. and the mixt. was stirred for 16 hrs. Solvent removal and recrystn. from MeOH gave 1.42 g 1-(4-octylphenyl)-3-(2,6-dichlorophenyl)urea (Ia) (68%) m.pt. 170-172°C.

(Ia) adminstered at 25 mg/kg/day for 5 days to male golden Syrian hamsters gave 49% inhibition of cholesterol in serum.(27pp1858 SAHDwgNo0/0).

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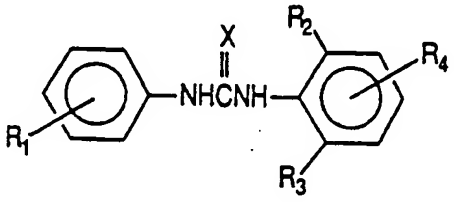
(54) Diphenylurea derivatives.

(57) Novel diphenylurea derivatives represented by the following formula (I):



(I)

wherein R_1 is an alkyl group of 5 to 18 carbon atoms, each of R_2 and R_3 is independently an alkyl group of 1 to 5 carbon atoms, an alkoxy group of 1 to 5 carbon atoms or a halogen atom, R_4 is hydrogen atom, an alkyl group of 1 to 5 carbon atoms, an alkoxy group of 1 to 5 carbon atoms or a halogen atom, and X is oxygen atom or sulfur atom, are provided.

The compounds are potent in reducing the cholesterol level in serum, and useful for treating hyperlipemia and atherosclerosis.

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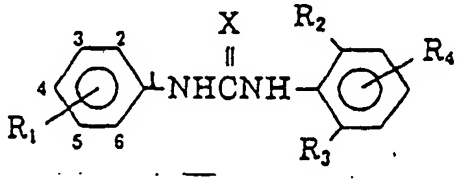
group, t-butoxy group, n-pentyloxy group, isopentyloxy group, sec-pentyloxy group, t-pentyloxy group, or neopentyloxy group. Furthermore, as the halogen atom, there may be mentioned fluorine atom, chlorine atom, or bromine atom.

In the formula (I), R_1 may preferably be a normal alkyl group of 6 to 10 carbon atoms, and more preferably, R_1 is present at 2- or 4-position of the benzene ring, and more preferably, R_4 is hydrogen atom.

The preferred examples of the compounds according to the present invention include those listed in the following Table 1.

Table 1



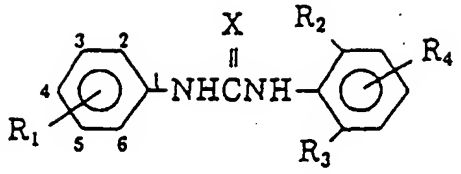
R_1	R_2	R_3	R_4	X
2-n-C_5H_{11}	i-C_3H_7	i-C_3H_7	H	O
2-n-C_5H_{11}	Cl	Cl	H	O
2-n-C_5H_{11}	CH_3	CH_3	4-CH_3	O
2-n-C_6H_{13}	C_2H_5	C_2H_5	H	O
2-n-C_6H_{13}	i-C_3H_7	i-C_3H_7	H	O
2-n-C_6H_{13}	Cl	Cl	H	O
2-n-C_6H_{13}	OCH_3	OCH_3	H	O
2-n-C_6H_{13}	CH_3	CH_3	4-CH_3	O
2-n-C_7H_{15}	C_2H_5	C_2H_5	H	O
2-n-C_7H_{15}	i-C_3H_7	i-C_3H_7	H	O
2-n-C_7H_{15}	F	F	H	O
2-n-C_7H_{15}	Cl	Cl	H	O
2-n-C_7H_{15}	OCH_3	OCH_3	H	O
2-n-C_7H_{15}	t-C_4H_9	CH_3	H	O

R_1	R_2	R_3	R_4	X
$2-n-C_9H_{19}$	$i-C_3H_7$	$i-C_3H_7$	H	O
$2-n-C_9H_{19}$	F	F	H	O
$2-n-C_9H_{19}$	Cl	Cl	H	O
$2-n-C_9H_{19}$	OCH_3	OCH_3	H	O
$2-n-C_9H_{19}$	C_2H_5	CH_3	H	O
$2-n-C_9H_{19}$	$sec-C_4H_9$	C_2H_5	H	O
$2-n-C_9H_{19}$	CH_3	CH_3	$4-CH_3$	O
$2-n-C_9H_{19}$	F	F	4-F	O
$2-n-C_9H_{19}$	Cl	Cl	4-Cl	O
$2-n-C_9H_{19}$	OCH_3	OCH_3	$4-OCH_3$	O
$2-n-C_{10}H_{21}$	C_2H_5	C_2H_5	H	O
$2-n-C_{10}H_{21}$	$i-C_3H_7$	$i-C_3H_7$	H	O
$2-n-C_{10}H_{21}$	Cl	Cl	H	O
$2-n-C_{10}H_{21}$	CH_3	CH_3	$4-CH_3$	O
$2-n-C_{11}H_{23}$	$i-C_3H_7$	$i-C_3H_7$	H	O
$2-n-C_{11}H_{23}$	Cl	Cl	H	O
$2-n-C_{11}H_{23}$	CH_3	CH_3	$4-CH_3$	O
$2-n-C_{12}H_{25}$	$i-C_3H_7$	$i-C_3H_7$	H	O
$2-n-C_{12}H_{25}$	Cl	Cl	H	O
$2-n-C_{12}H_{25}$	CH_3	CH_3	$4-CH_3$	O
$2-n-C_{13}H_{27}$	$i-C_3H_7$	$i-C_3H_7$	H	O
$2-n-C_{13}H_{27}$	Cl	Cl	H	O

R_1	R_2	R_3	R_4	X
3-n-$C_{11}H_{23}$	i-C_3H_7	i-C_3H_7	H	O
3-n-$C_{12}H_{25}$	i-C_3H_7	i-C_3H_7	H	O
3-n-$C_{13}H_{27}$	i-C_3H_7	i-C_3H_7	H	O
3-n-$C_{14}H_{29}$	i-C_3H_7	i-C_3H_7	H	O
3-n-$C_{15}H_{31}$	i-C_3H_7	i-C_3H_7	H	O
3-n-$C_{16}H_{33}$	i-C_3H_7	i-C_3H_7	H	O
3-n-$C_{17}H_{35}$	i-C_3H_7	i-C_3H_7	H	O
3-n-$C_{18}H_{37}$	i-C_3H_7	i-C_3H_7	H	O
4-n-C_5H_{11}	i-C_3H_7	i-C_3H_7	H	O
4-n-C_5H_{11}	Cl	Cl	H	O
4-n-C_5H_{11}	CH_3	CH_3	4-CH_3	O
4-n-C_6H_{13}	C_2H_5	C_2H_5	H	O
4-n-C_6H_{13}	i-C_3H_7	i-C_3H_7	H	O
4-n-C_6H_{13}	Cl	Cl	H	O
4-n-C_6H_{13}	OCH_3	OCH_3	H	O
4-n-C_6H_{13}	CH_3	CH_3	4-CH_3	O
4-n-C_7H_{15}	C_2H_5	C_2H_5	H	O
4-n-C_7H_{15}	i-C_3H_7	i-C_3H_7	H	O
4-n-C_7H_{15}	F	F	H	O
4-n-C_7H_{15}	Cl	Cl	H	O
4-n-C_7H_{15}	OCH_3	OCH_3	H	O
4-n-C_7H_{15}	t-C_4H_9	CH_3	H	O

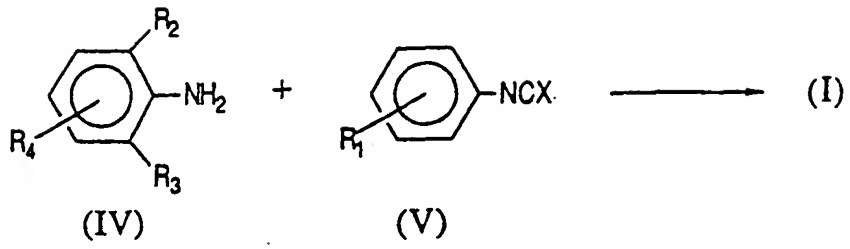
R_1	R_2	R_3	R_4	X
4 – n – C_9H_{19}	i – C_3H_7	i – C_3H_7	H	O
4 – n – C_9H_{19}	F	F	H	O
4 – n – C_9H_{19}	Cl	Cl	H	O
4 – n – C_9H_{19}	OCH_3	OCH_3	H	O
4 – n – C_9H_{19}	C_2H_5	CH_3	H	O
4 – n – C_9H_{19}	sec – C_4H_9	C_2H_5	H	O
4 – n – C_9H_{19}	CH_3	CH_3	4 – CH_3	O
4 – n – C_9H_{19}	F	F	4 – F	O
4 – n – C_9H_{19}	Cl	Cl	4 – Cl	O
4 – n – C_9H_{19}	OCH_3	OCH_3	4 – OCH_3	O
4 – n – $C_{10}H_{21}$	C_2H_5	C_2H_5	H	O
4 – n – $C_{10}H_{21}$	i – C_3H_7	i – C_3H_7	H	O
4 – n – $C_{10}H_{21}$	Cl	Cl	H	O
4 – n – $C_{10}H_{21}$	CH_3	CH_3	4 – CH_3	O
4 – n – $C_{11}H_{23}$	i – C_3H_7	i – C_3H_7	H	O
4 – n – $C_{11}H_{23}$	Cl	Cl	H	O
4 – n – $C_{11}H_{23}$	CH_3	CH_3	4 – CH_3	O
4 – n – $C_{12}H_{25}$	i – C_3H_7	i – C_3H_7	H	O
4 – n – $C_{12}H_{25}$	Cl	Cl	H	O
4 – n – $C_{12}H_{25}$	CH_3	CH_3	4 – CH_3	O
4 – n – $C_{13}H_{27}$	i – C_3H_7	i – C_3H_7	H	O
4 – n – $C_{13}H_{27}$	Cl	Cl	H	O

Table 2



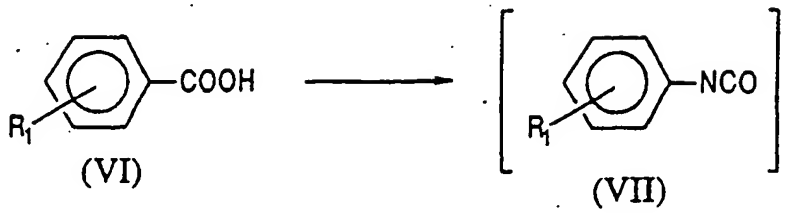
R_1	R_2	R_3	R_4	X
2-n-C_6H_{13}	i-C_3H_7	i-C_3H_7	H	S
2-n-C_7H_{15}	i-C_3H_7	i-C_3H_7	H	S
2-n-C_8H_{17}	i-C_3H_7	i-C_3H_7	H	S
2-n-C_9H_{19}	i-C_3H_7	i-C_3H_7	H	S
2-n-$C_{10}H_{21}$	i-C_3H_7	i-C_3H_7	H	S
3-n-C_6H_{13}	i-C_3H_7	i-C_3H_7	H	S
3-n-C_7H_{15}	i-C_3H_7	i-C_3H_7	H	S
3-n-C_8H_{17}	i-C_3H_7	i-C_3H_7	H	S
3-n-C_9H_{19}	i-C_3H_7	i-C_3H_7	H	S
3-n-$C_{10}H_{21}$	i-C_3H_7	i-C_3H_7	H	S
4-n-C_5H_{11}	i-C_3H_7	i-C_3H_7	H	S
4-n-C_6H_{13}	i-C_3H_7	i-C_3H_7	H	S
4-n-C_6H_{13}	Cl	Cl	3-CH_3	S
4-n-C_7H_{15}	i-C_3H_7	i-C_3H_7	H	S
4-n-C_7H_{15}	Cl	Cl	4-Cl	S
4-n-C_8H_{17}	C_2H_5	C_2H_5	H	S
4-n-C_8H_{17}	i-C_3H_7	i-C_3H_7	H	S
4-n-C_8H_{17}	OCH_3	OCH_3	H	S

Method A-2

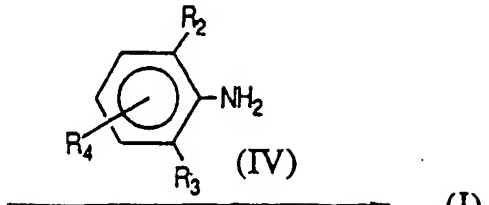


(IV) (V)

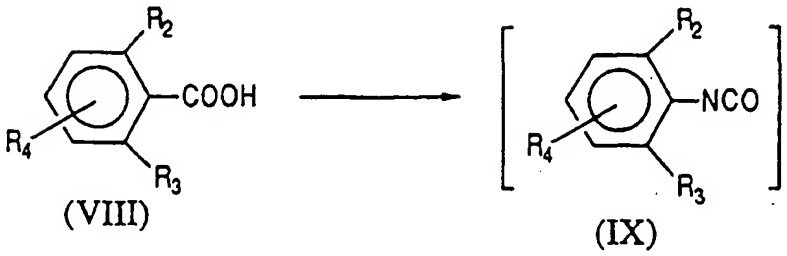
Method B-1



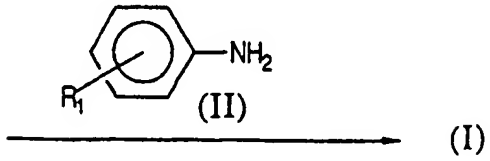
(VI) (VII)



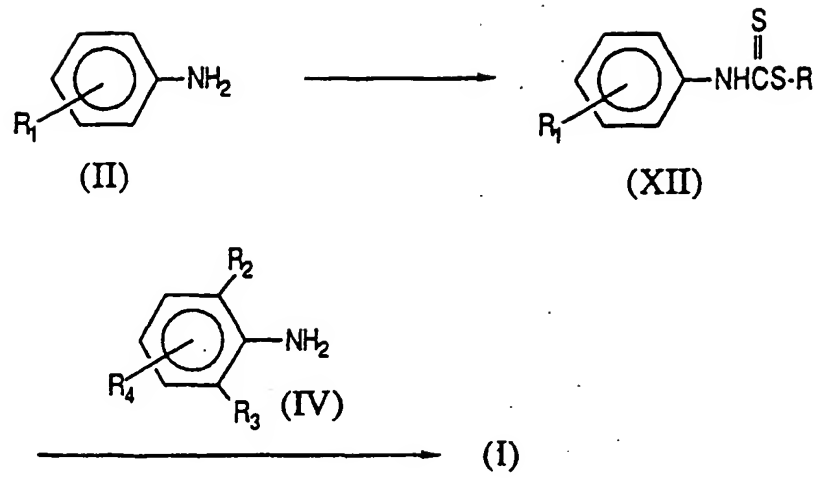
Method B-2



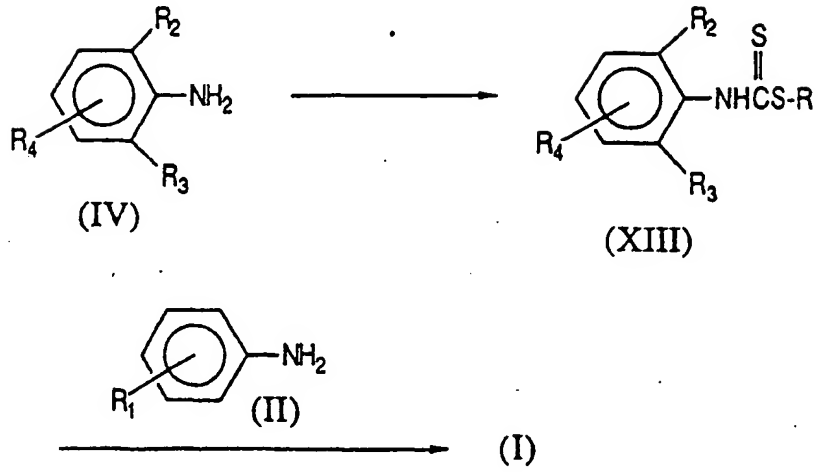
(VIII) (IX)



Method D-1



Method D-2



wherein, R_1, R_2, R_3, R_4 and X are the same as defined above, Y is a leaving group such as chlorine atom or aryloxy group, and R is an alkyl group of 1 to 3 carbon atoms.

According to Method A-1, the compound (I) of the invention is prepared by reacting an aniline derivative of general formula (II) with a phenyl isocyanate or phenyl isothiocyanate derivative of the formula (III) at a temperature range of 0 °C to ca. 150 °C in an inert solvent such as benzene, toluene, xylene, hexane, heptane, tetrahydrofuran (THF), dioxane, ether, or N,N-dimethylformamide. Method A-2 comprises the preparation of the compound (I) of the invention by reacting an aniline derivative of formula (IV) with a phenyl isocyanate or phenyl isothiocyanate of the formula (V) in a similar manner to Method A-1.

According to Method B-1, the compound (I) of the invention wherein X is oxygen is prepared by converting a benzoic acid derivative of the formula (VI) into a phenyl isocyanate derivative of the formula (VII) using different procedures, followed by reacting an aniline derivative of the formula (IV) with the resulting isocyanate at a temperature range of 0 °C to ca. 150 °C. The conversion of the benzoic acid derivative of the formula (VI) into the phenyl isocyanate derivative of the formula (VII) may be achieved, for example, by treating the benzoic acid derivative with DPPA (diphenoxy phosphoryl azide) in the presence of an inert amine such as triethylamine at a temperature range of room temperature to ca. 150 °C in an inert solvent such as benzene, toluene or xylene. Method B-2 comprises the preparation of the compound (I) of

prepared as above.

Example 2

Preparation of 1-(4-nonylphenyl)-3-(2.6-diisopropylphenyl)urea (Compound No. 19 in Table 3)

To a 10 ml toluene solution of 1.0 g (4.04 mmol) of 4-nonylbenzoic acid was added 0.66 ml (4.28 mmol) of triethylamine. After stirring at room temperature for 15 minutes, 0.89 ml (4.12 mmol) of DPPA (diphenoxy phosphoryl azide) was added to the mixture. The whole was heated for 2 hours under reflux and then cooled to room temperature. After the addition of 0.77 ml (4.08 mmol) of 2,6-diisopropylaniline, the reaction mixture was stirred for 16 hours and then concentrated. The residue was purified by subjecting it to column chromatography over silica gel (eluent: n-hexane/chloroform = 1/1) to give 1.07 g (62% yield) of 1-(4-nonylphenyl)-3-(2,6-diisopropylphenyl)urea, the physical properties of which being shown in the following Table 3. The compounds No. 5, No.6, No. 7, No. 8, No.9, No. 10, No. 12, No. 16, No. 20, No. 21, No. 22, No. 23, and No. 26 listed in Table 3 were similarly prepared as above.

Example 3

Preparation of 1-(4-octylphenyl)-3-(2.4.6-trichlophenyl)urea (Compound No. 3 in Table 3)

A 10 ml methylene chloride solution of 1.0 g (5.09 mmol) of 2,4,6-trichloroaniline was added dropwise over 2 minutes to a 10 ml methylene chloride solution of 0.6 ml (4.97 mmol) of trichloromethyl chloroformate cooled to 5-6 °C. After stirring at 5-6 °C for 2 hours, the mixture was added with 1.04 g (5.06 mmol) of 4-octylaniline and then stirred at room temperature for 16 hours. The reaction mixture was extracted with chloroform, and washed with an aqueous saturated solution of sodium hydrogen carbonate and an aqueous saturated solution of sodium chloride, successively. The organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was recrystallized from a mixed solvent of n-heptane and chloroform to give 0.95 g (43% yield) of 1-(4-octylphenyl)-3-(2,4,6-trichlorophenyl)urea, the physical properties of which being shown in the following Table 3. The compounds No. 4 and No. 11 listed in Table 3 were similarly prepared as above.

Example 4

Preparation of 1-(4-octylphenyl)-3-(2,6-diisopropylphenyl)thiourea (Compound No. 15 in Table 3)

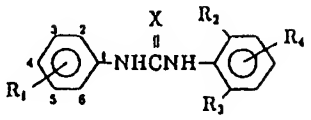
To a 10 ml N,N-dimethylformamide solution of 1.0 g (4.87 mmol) of 4-octylaniline was added 1.07 g (4.88 mmol) of 2,6-diisopropyl thioisocyanate, and the whole was stirred at 100 °C for 20 hours. The reaction mixture was extracted with ethyl acetate, washed with an aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by subjecting it to column chromatography over silica gel (eluent: ethyl acetate/n-hexane = 3/97) to give 0.96 g (46% yield) of 1-(4-octylphenyl)-3-(2,6-diisopropylphenyl)thiourea. The physical properties of the compound are shown in the following Table 3.

Example 5

Preparation of 1-(2-hexylphenyl)-3-(2.6-diisopropylphenyl)urea (Compound No. 24 in Table 3)

To a 5 ml n-hexane solution of 0.42 g (2.35 mmol) of 2-hexylaniline was added 5 ml (2.35 mmol) of a hexane solution of 0.47M 2,6-diisopropylphenyl isocyanate at room temperature and the whole was stirred for 16 hours. The precipitated crystals were collected by filtration to give 0.55 g (61% yield) of 1-(2-

Table 3



Compound No.	R_1	R_2	R_3	R_4	X	IR (KBr) (cm^{-1})	NMR ($CDCl_3$) (δ)	Melting point (°C)
1	-4-C_8H_{17}	-F	-F	-H	O	3340, 1645, 1595 1540	0.88 (3H, t), 1.29 (10H, m), 1.57 (2H, m) 2.55 (2H, t), 6.35 (1H, bs), 6.81 (1H, bs) 6.91 (2H, m), 7.10 (3H, m), 7.22 (2H, m)	173 - 175
2	-4-C_8H_{17}	-Cl	-Cl	-H	O	3340, 1645, 1595 1540	0.88 (3H, t), 1.29 (10H, m), 1.57 (2H, m) 2.55 (2H, t), 6.35 (1H, bs), 6.81 (1H, bs) 6.96 (2H, m), 7.10 (3H, m), 7.22 (2H, m)	170 - 172
3	-4-C_8H_{17}	-Cl	-Cl	-4-Cl	O	3370, 3330, 2950 1655, 1610, 1575 1550	0.88 (3H, t), 1.27 (10H, m), 1.51 (2H, m) 2.45 (2H, t), 6.81 (2H, d), 7.00 (2H, d) 7.13 (2H, s), 7.21 (1H, s), 7.52 (1H, s)	192 - 193
4	-4-C_8H_{17}	-Br	-Br	-H	O	3300, 2940, 1640 1600, 1550	0.87 (3H, t), 1.27 (10H, m), 1.63 (2H, m) 2.52 (2H, t), 6.72 (1H, s), 6.90 (1H, t) 6.99 (1H, s), 7.07 (2H, d), 7.24 (2H, d) 7.49 (2H, d)	181 - 183
5	-4-C_8H_{17}	-CH_3	-CH_3	-H	O	3310, 2940, 1635 1595, 1545	0.87 (3H, t), 1.26 (10H, m), 1.58 (2H, m) 2.33 (6H, s), 2.53 (2H, t), 5.98 (1H, bs) 6.09 (1H, bs), 7.09 (2H, d), 7.20 (5H, m)	164 - 165
6	-4-C_8H_{17}	-CH_3	-CH_3	-4-CH_3	O	3310, 2925, 1640 1600, 1550	0.87 (3H, t), 1.26 (10H, m), 1.55 (2H, m) 2.29 (6H, s), 2.31 (3H, s), 2.53 (2H, t) 5.77 (1H, bs), 6.08 (1H, bs), 6.96 (2H, s) 7.09 (2H, s), 7.23 (3H, m)	165 - 167
7	-4-C_6H_{17}	-CH_2CH_3	-CH_2CH_3	-H	O	3320, 2940, 1644 1600, 1558, 1507	0.87 (3H, t), 1.23 (16H, m), 1.55 (2H, bs) 2.52 (2H, t), 3.35 (2H, bt), 6.10 (2H, bs) 7.21 (7H, m)	125 - 127
8	-4-C_8H_{17}	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3450, 3320, 2940 1647, 1605, 1559 1520	0.87 (3H, t), 1.23 (22H, m), 1.54 (2H, bs) 2.52 (2H, t), 3.35 (2H, bt), 6.10 (2H, bs) 7.21 (7H, m)	120 - 122

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Table 3 (Contd.)

Compound No.	R_1	R_2	R_3	R_4	X	IR (KBr) (cm^{-1})	NMR ($CDCl_3$) (δ)	Melting point (°C)
18	-4-C_7H_{15}	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3440, 3330, 2940, 1648, 1605, 1558, 1520	0.87 (3H, t), 1.22 (20H, m), 1.54 (2H, bt), 2.51 (2H, t), 3.35 (2H, bt), 6.42 (2H, bs), 7.19 (7H, m)	142-143
19	-4-C_9H_{19}	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3320, 2950, 1640, 1600, 1555	0.87 (3H, t), 1.20 (24H, m), 1.57 (2H, m), 2.52 (2H, t), 3.53 (2H, m), 5.87 (1H, s), 6.01 (1H, bs), 7.08 (2H, d), 7.16 (4H, m), 7.36 (1H, m)	106-108
20	-4-$C_{10}H_{21}$	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3330, 2945, 1640, 1600, 1555	0.87 (3H, t), 1.24 (26H, m), 1.62 (2H, m), 2.52 (2H, t), 3.53 (2H, m), 6.05 (2H, bs), 7.04 (2H, d), 7.19 (2H, d), 7.26 (2H, d), 7.36 (1H, m)	90-92
21	-4-$C_{12}H_{25}$	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3330, 2950, 1640, 1600, 1560	0.87 (3H, t), 1.25 (30H, m), 1.58 (2H, m), 2.52 (2H, t), 3.37 (2H, m), 6.05 (2H, bs), 7.06 (2H, d), 7.20 (2H, d), 7.39 (1H, m)	89-90
22	-4-$C_{15}H_{31}$	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3330, 2940, 1640, 1600, 1555	0.88 (3H, t), 1.25 (36H, m), 1.57 (2H, m), 2.52 (2H, t), 3.35 (2H, m), 5.87 (1H, s), 6.01 (1H, bs), 7.05 (2H, d), 7.20 (2H, d), 7.26 (2H, d), 7.38 (1H, m)	91-93
23	-4-$C_{18}H_{37}$	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3310, 2930, 1640, 1600, 1560	0.86 (3H, t), 1.25 (42H, m), 1.54 (2H, m), 2.52 (2H, t), 3.35 (2H, m), 6.10 (2H, bs), 7.04 (2H, d), 7.19 (2H, d), 7.26 (2H, d), 7.35 (1H, m)	97-98.5
24	-2-C_6H_{13}	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3320, 2940, 1640, 1540	0.86 (3H, t), 1.22 (20H, m), 2.13 (2H, bs), 3.38 (2H, bs), 6.05 (1H, bs), 6.18 (1H, bs), 7.03 (2H, bs), 7.24 (4H, m), 7.34 (1H, m)	189-191
25	-3-C_6H_{13}	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3300, 2960, 1640, 1610, 1560	0.86 (3H, t), 1.26 (18H, m), 1.57 (2H, m), 2.52 (2H, t), 3.35 (2H, m), 5.96 (2H, bs), 6.86 (1H, d), 7.10 (3H, m), 7.26 (2H, m), 7.39 (1H, t)	129-131
26※	-4-$C(CH_3)_3$	-$CH(CH_3)_2$	-$CH(CH_3)_2$	-H	O	3440, 3320, 2955, 1644, 1602, 1550	1.28 (21H, m), 3.35 (2H, m), 6.12 (2H, bs), 7.28 (7H, m)	

※ Comparative Example

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that in Table 3.

Table 5

Compound No.	ACAT inhibitory activity $IC_{50}(\mu M)$
8	0.004
17	0.011
18	0.006
19	0.010
20	0.012

Test example 3

Acute toxicity test

A compound according to the present invention suspended in a 1% tragacanth solution was administrated orally to SD male and female rats. Then, the number of fatal rats was counted during seven day observation. The LD_{50} value is shown in the following Table 6, the compound number corresponding to that in the above Table 3.

Table 6

Compound No.	LD_{50} (mg/kg P.O.)
8	>2000

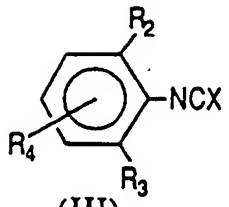
Examples of formulation

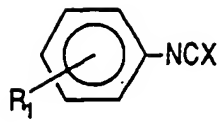
(1) Tablet

The following ingredients were mixed according to the usual manner and compressed to a tablet using a conventional machine.

Compound No. 8	10 mg
Crystalline cellulose	21 mg
Corn starch	33 mg
Lactose	65 mg
Magnesium stearate	1.3 mg

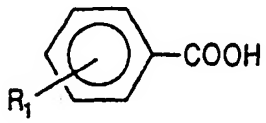
(2) Soft capsule

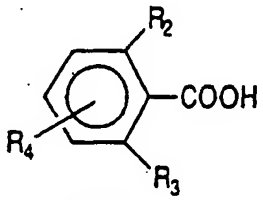

(III)


(V)

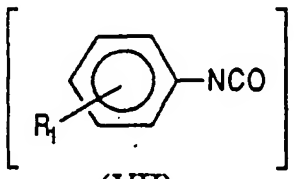
wherein, R_1, R_2, R_3, R_4 and X are the same as defined above, in an inert solvent at a temperature range of 0 ° C to ca. 150 ° C;

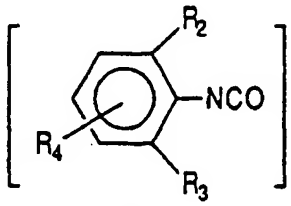
B) converting a benzoic acid derivative of the following formula (VI) [or (VIII)]


(VI)


(VIII)

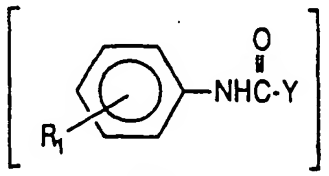
wherein, R_1, R_2, R_3 and R_4 are the same as defined above, into a corresponding phenyl isocyanate derivative of the following formula (VII) [or (IX)]

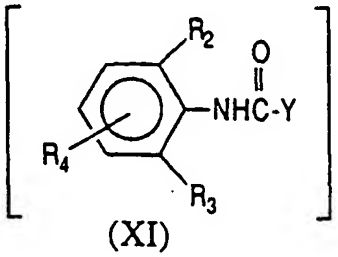

(VII)


(IX)

wherein, R_1, R_2, R_3 and R_4 are the same as defined above, by treating the benzoic acid derivative with DPPA (diphenoxy phosphoryl azide) in the presence of an inert amine at a temperature range of room temperature to ca. 150 ° C in an inert solvent, and reacting an aniline derivative of the formula (IV) [or (II)] with the isocyanate (VII) [or (IX)] at a temperature range of 0 ° C to ca. 150 ° C;

C) treating an aniline derivative of the formula (II) [or (IV)] with an activated derivative of carbonic acid such as phosgene or phenyl chloroformate to give a reactive intermediate of the following formula (X) [or (XI)] such as an arylcarbamyl chloride or an aryl ester of arylcarbamic acid,


(X)


(XI)

wherein, R_1, R_2, R_3 and R_4 are the same as defined above and Y is a leaving group such as chlorine